Crosslink Polyacrilic Resin Based Levocetirizine Melt-In-Mouth Tablets

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ABSTRACT

Purpose of undertaken project was to formulate crosslink polyacrilic resin based, technologically optimised, melt-in-mouth tablet (MIMT) containing 5 mg of Levocetirizine Dihydrochloride that was intended to disintegrate rapidly in the oral cavity so as to form a stabilised dispersion and possessing adequate physicochemical stability. Different grades of crosslink polyacrilic resin were utilised to prepare MIMTs; employing complexation technique; and using additives like Mannitol DC, Ac-di-sol, Avicel-pH 112, Tusil pinapple, Saccharine sodium, Aerosil and Magnesium stearate. MIMTs were evaluated for compliance to pharmacopoeial specifications. From *in-vitro* dissolution profile plot, values for the kinetic constant and the regression coefficient of model-dependent approaches were determined to find the best fit release kinetic model while from *in-vitro* dissolution profile data the difference factor, the similarity factor and the indices of rescigno of model-independent approaches were determined for comparing pair of *in-vitro* dissolution profiles. MIMTs of levocetirizine was successfully developed complying pharmacopoeial specifications, with adequate stability at room temperature.

KEY WORDS: Melt-in-mouth tablet, levocetirizine hydrochloride, pharmacopoeial, specification.

INTRODUCTION

Historically oral route of administration was still preferred not only due to the ease of administration, the self-medication and the patient compliance [1-3] but also due to their compact nature; stability and low cost; ease of packaging, transport, and manufacture;[4] and possesses acceptance up to 50-60% of total dosage forms.[1] Now a day MIMTs were very much popular and indicated for dysphagic, geriatric, paediatric, bed-ridden, travelling and psychotic patients who were unable/uncooperative to swallow conventional oral formulations and also for improving palatability of bitter drugs.[1, 5-6] MIMTs was synonym for 'Mouth dissolving', 'Orally disintegrating', 'Orodispersible', 'Rapimelts', 'Porous', 'Quick dissolving' tablets and 'Fast dissolving drug delivery system',[1] etc.; and these terminology had been official in pharmacopoeia of several countries.[6-9]

Rhinitis possesses cardinal feature of inflammation of the upper airway while some forms of rhinitis do not involve inflammation rather was symptomatically referred as nasal congestion, pruritus, sneezing, anterior or posterior rhinorrhea. Rhinitis may be of allergic and non allergic origin and the reaction was typically associated with an early phase followed by a late phase response. Early phase of allergic rhinitis occurs within minutes of allergen exposure associated with activation of tissue mast cells sensitised by IgE antibodies.[10-11] In addition to the nasal and ocular symptoms of the disease, allergic rhinitis was associated with a higher burden of asthma and sinusitis. It also affects multiple areas related to quality of life, including quality of sleep, mood and energy level, work effectiveness, and even sexual function.[10-11] Antihistamines prescribed alone or in combination with intranasal corticosteroids to control symptoms of rhinitis, and conjunctival itching and redness.[11] Numbers of first- and second-generation antihistamines were available for oral and topical administration.[12] Levocetirizine, the active isomer of its parent compound, cetirizine, was one of the newest second-generation antihistamines. Single dose of levocetirizine had been found to suppress the cutaneous allergic response to a significantly greater extent with respect to drugs of its class and also was effective in the treatment of nasal congestion.[12] Dihydrochloride form of levocetirizine was official as Levocetirizine Hydrochloride (LH) in Indian Pharmacopoeia (IP) 2007.[13] Above principles apprehend a strong need to develop MIMT of levocetirizine complying pharmacopoeial specifications having adequate stability.

MATERIALS

Levocetirizine hydrochloride and Doshion p-542 were kindly donated by Medopharm Pvt. Ltd. (Chennai, India). Mannitol DC, Ac-di-sol, Avicel pH 112, Tusil pinapple, Saccarine sodium, Aerosil, Magnesium stearate were

free gift samples from Indoco Remedies Limited (Mumbai, India), and all other chemicals and solvents of laboratory grade purchased locally.

METHODS

IP-2007 specification compliance study of LH

Sample of LH was subjected to IP 2007 specification compliance study.[13]

Preformulation study

Preformulation study of LH was carried out for the per cent w/w loss on drying (% LOD), the particle size distribution, the flow property, and the drug-excipient compatibility; as described bellow, in triplicate and mean value was considered.

Correctly blended LH was subjected for per cent loss on drying study using infrared moisture balance (Citizen MB-50 X, Japan), at 105^{o}C.[13] Particle size distribution study was performed with about 25 g of accurately weighed LH using nest of dried sieves having mesh size of 20, 40, 60, 80 and 100; arranged chronologically in an electromagnetic sieve shaker (Electrolab, EMS-8, Mumbai, India) and agitating for 15 min.[14] Frequency distribution curve was plotted between powder weights versus size range. From the result of study parameters; Angle of repose, Carr's index, and Hausner ratio; flow property of LH was determined.[14] LH was mixed independently with excipients in 1:1 ratio and individual sets of each mixture were kept for 4 weeks at 40ºC ± 2ºC/75 ± 5% RH in a stability analysis chamber (Darwin Chambers Company, St Louis, USA). The physicochemical compatibilities of the drug and the proposed excipients were analysed from observed data of organoleptic properties, moisture content, related substance, and assay; from pooled sample at 1 w interval.

Formulation development of Levocetirizine MIMTs

Development of LH-resin complex

LH was complexed with different grade of crosslink polyacrilic resin (Doshion p-542, Doshion p-542C and Doshion p-542D) in 1:1, 1:2 and 1:3 ratio (LH-to-resin). Accurately weighed resin was stirred with sufficient quantity of water in a clean dry stainless steel container, for 15 minutes with a mechanical stirrer. LH was slowly added with slow and constant stirring followed by stirring for another 15 minutes. The container was kept aside in a closed condition for 12 h so as to settle down the LH-resin complex followed by decanting and preserving the supernatant water layer (Decanted Water). The LH-resin complex were sifted through 40 mesh sieve and dried at 50ºC till the % LOD value reaches 3-4%.

Performance evaluation of LH-resin complex

Performances of LH-resin complexes were evaluated so as to select suitable grade of the resin and the LH-to-resin ratio for development of MIMT formulas and was accessed from the dissolution profile of LH-resin complex in 0.1 N HCL and Phosphate Buffer pH 6.8 using HPLC.[13]

Preparation of pre-lubricated blend for compression

MIMTs formulations was developed with LH-Doshion p-542 resin complex at a LH-to-resin ratio of 1:3, as selected grade of the resin and the ratio, release less amount of LH in Phosphate Buffer pH 6.8 while appreciably higher amount at pH 1.2 of stomach (Table-1) and highest performances. LH-Doshion p-542 resin complex (at LH-to-resin ratio of 1:3) was prepared as per the method of development in LH-resin complex step, following the formula of Table-2. Calculated quantity of excipient, following the formula of Table-2, were weighed separately after sifting them through 60 mesh sieve excluding Mannitol DC that was sifted with 20 mesh sieve. The excipients were blended with LH-resin complex following direct compression and wet granulation technique.

Table-1: Comparative *in-vitro* dissolution profile of Levocetirizine Hydrochloride from different drug-resin complexes.

Resin used in preparing the drug-resin complex	**Dissolution medium**	**Percent levocetirizine released per unit time (min)**				
		1	2	3	4	5
Doshion p542	Phosphate Buffer pH 6.8	4.65	10.23	18.39	25.86	30.34
	0.1 N HCL pH 1.2	12.9	18.35	30.51	35.21	48.37
Doshion p542C	Phosphate Buffer pH 6.8	7.24	14.23	18.69	22.23	48.62
	0.1 N HCL pH 1.2	18.3	31.5	38.3	59.9	62.23
Doshion p542D	Phosphate Buffer pH 6.8	9.7	16.9	22.4	30.8	38.68
	0.1 N HCL pH 1.2	22.29	28.36	36.84	46.31	53.93

Table-2: Tablet formulation formula of all formulation batches.

S. No.	Content	Quantity of ingredient (mg)				
1	**Formulation code**	**F1**	**F2**	**F3**	**F4**	**F5**
2	**Prelubrication Stage**					
	Levocetirizine Hydrochloride IP	5	5	5	5	5
	Doshion p542 IHS	15	15	15	15	15
	Demineralised Water	q.s.	q.s.	q.s.	q.s.	q.s.
	Decanted Water	----	q.s.	q.s.	q.s.	q.s.
	Mannitol IP (Direct Compressible)	73	73	67	57	51
	Croscarmellose Sodium IP (Ac-di sol)	5	5	10	20	30
	Microcrystalline Cellulose IP (Avicel pH 112)	65	65	60	60	56
	Tusil Pinapple IHS	1	1	1.5	1.5	1.5
	Saccarine Sodium IP	5	5	10	10	10
3	**Lubrication stage**					
	Colloidal Silicone Dioxide IP (Aerosil)	0.5	0.5	0.5	0.5	0.5
	Magnesium Stearate IP	0.5	0.5	1	1	1
	TWUT	170	170	170	170	170

Where, IP stands for Indian Pharmacopoeia 2007, TWUT for Theoretical weight of tablets, IHS for In-house-specifications, and q.s. for quantity sufficient.

Direct compression technique (for formulation batch F1): Dried and sized LH-Doshion p-542 resin complex, Decanted Water; and all other excipients, excluding Magnesium stearate, were blended geometrically in a double cone blender, followed by final blending for 15 minutes.

Wet granulation technique (for formulation batches F2-F5): Dried and sized LH-Doshion p-542 resin complex, Mannitol DC, and half quantity of the Ac-di-sol and the Avicel pH 112 were blended in double cone blender for 15 min. To the powder blend Decanted Water was added slowly in a planetary mixer (Kenwood, India) setting speed of the blending shaft at 200 r/min followed by addition of sufficient quantity of Demineralised Water, till a damp mass was obtained; and operated for next 15 minutes. The damp mass was then sifted with 10 mesh sieve followed by drying at 50-60ºC till the % LOD value reaches 3-4%. The dried granules were sized with 20 mesh sieve, followed by blending with Trusil pinapple, Saccharine sodium and rest quantity of the Ac-di-sol and the Avicel pH 112, in double cone blender, for 15 min.

Physical characterization of pre-lubricated blend

Physical characterisations of dried granules of all formulation batches were carried out by studying parameters namely: flow property, % LOD and particle size distribution, following the method as employed for LH.

Lubrication stage processing of pre-lubricated blend

Calculation for Magnesium stearate was done as per the formula of Table-2 for the calculated number of tablets. Calculated quantity of Magnesium stearate was weighed accurately after sifting through 60 mesh sieve and was blended in a planetary mixer for 2 minutes followed by collecting the product in a tare polyethylene lined collection vessel and were stored at room temperature for compression.

Compression of MIMTs

MIMTs of all formulation batches were compressed separately using lubricated granules of specific formulation batch, separately. Tablets were compressed employing 16 station rotary tablet compression machine (Labindia, India) using 6.0 mm round standard plain punches, weighing 170 mg and keeping hardness between 40-50 Newton.

Evaluation of MIMTs

Tablets were subjected for evaluation of parameter namely: appearance, shape and size, resistance to crushing of tablet (hardness), friability, uniformity of content, wetting time, content of active ingredient, impurity profile, *in-vitro* disintegration time, uniformity of dispersion, *in-vitro* dissolution, and *in-vitro* drug dissolution profile.

The general appearance, size, shape, colour, surface texture and elegance of MIMTs were observed visually. Hardness of ten MIMTs was measured using tablet hardness tester (Dr Schleuniger Pharmatron AG, Pharmatron 8M, Switzerland) and the mean value was reported in Newton.[14] Diameter and thickness of ten MIMTs were measured using digital vernier calliper (Mitutoyo America Corporation, CD-6 INCH CSX, USA), and the mean value was reported in mm.[1] Friability test of MIMTs was performed with friability tester (Electrolab, EF-1W, Mumbai, India) [13] and per cent loss in weight (friability) was calculated using following equation. Disintegration time of MIMTs was determined using disintegration test apparatus (Labindia, India).[15] Uniformity of content test was performed following liquid chromatography as described in assay.[13]

$$\text{Friability (\% w/w)} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

Wetting time

A piece of tissue paper that had been folded twice was placed in Petri-dish having internal diameter of 6.5 cm containing 6 ml of Phosphate Buffer pH 6.8. Time required for complete wetting of tablet was noted after placing tablet on the paper. An average of six trials was determined.[16]

Content of active ingredient

Content of active ingredient (assay) of MIMTs was carried out following liquid chromatography using Shimadzu LC-2010AHT, Shimadzu Corporation, Japan.[13] Reference solution was prepared from *levocetirizine dihydrochloride RS* (the standard) while test solution from a powder blend obtained by crushing 20 tablets to powder. The percentage of LH present in each tablet was calculated using following equation.

$$\text{Levocetirizine HCl (in \% w/w)} = \frac{\text{Spl area}}{\text{Avg Std area}} \times \frac{\text{Std wt}}{100} \times \frac{5}{25} \times \frac{100}{\text{Spl wt}} \times \frac{\text{Std purity}}{100} \times \frac{100}{5} \times \frac{\text{Avg wt}}{\text{Label claim}}$$

Where, Spl stands for sample, Abs for absorbance, wt. for weight, and Std for standard.

Test for related substance (impurity profile)

Related substance test of MIMTs was done following liquid chromatography using Shimadzu-LC2010 AHT.[13] Reference solution was prepared from *lamotrigine RS* while test solution was prepared from a powder blend obtained by crushing 20 tablets to powder. Separately 20 µl of the reference solution and the test solution was injected, the chromatogram was recorded. Response for the secondary peaks was measured and the result was calculated by comparison and employing following equations.

$$\text{Impurity area} = \frac{\text{Any individual impurity area}}{\text{Reference solution area}} \times 1.0$$

$$\text{Total impurities area} = \frac{\text{Total impurities area}}{\text{Reference solution area}} \times 1.0$$

In-vitro *dissolution test*

In-vitro dissolution test was performed using IP dissolution test apparatus II (Electrolab, TDT-08L, Mumbai, India) at 37 ± 0.5°C and 50 rpm, containing 900 ml of Phosphate Buffer pH 6.8.[13]

In-vitro *drug dissolution profile study*

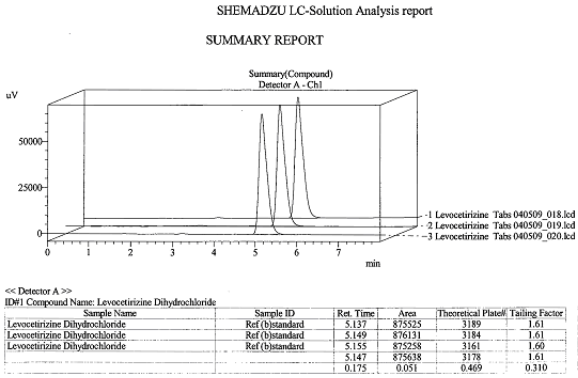
Drug dissolution profile study of MIMTs was performed using IP dissolution test apparatus II at 37 ± 0.5°C and 50 r/min, containing 900 ml of 0.1N HCl (a discriminatory dissolution medium for LH).[17] Five ml of sample solution was withdrawn at predetermined time interval followed by immediate replacement with an equal volume of fresh dissolution medium. The sample was filtered through 0.45 µm PVDF filter membrane. Drug content of samples (filtrate) were analysed using UV-Vis spectrophotometer (Perkin Elmer, Lambda 25, USA) at 231 nm wavelength, with reference to that of *levocetirizine dihydrochloride RS* (the standard) in same dissolution medium.[17] Percentage of LH was calculated using following equation.

$$\text{Levocetirizine HCl (Release in \% w/w)} = \frac{\text{Spl Abs}}{\text{Std Abs}} \times \frac{\text{Std wt}}{100} \times \frac{5}{50} \times \frac{900}{1} \times \frac{50}{2} \times \frac{\text{Std purity}}{100} \times \frac{100}{\text{Label claim}}$$

Where, Spl stands for sample, Abs for absorbance, wt for weight, and Std for standard.

For compliance of pharmacopoeial requirement related to dissolution profile 6 MIMTs from each formulation batch were subjected and average was considered for comparison and statistical analysis of dissolution profiles.

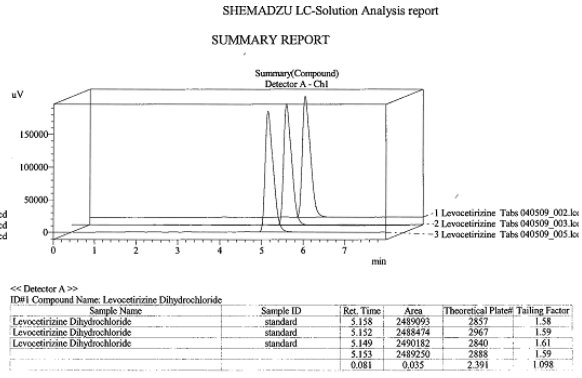
Figure 1: HPLC chromatograms.



<< Detector A >>
ID#1 Compound Name: Levocetirizine Dihydrochloride

Sample Name	Sample ID	Ret. Time	Area	Theoretical Plate#	Tailing Factor
Levocetirizine Dihydrochloride	Ref (b)standard	5.137	875525	3189	1.61
Levocetirizine Dihydrochloride	Ref (b)standard	5.149	876131	3184	1.61
Levocetirizine Dihydrochloride	Ref (b)standard	5.155	875258	3161	1.60
		5.147	875638	3178	1.61
		0.175	0.051	0.469	0.310

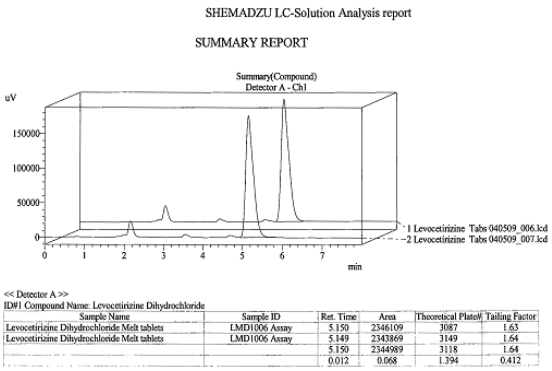
Figure 1(a)



<< Detector A >>
ID#1 Compound Name: Levocetirizine Dihydrochloride

Sample Name	Sample ID	Ret. Time	Area	Theoretical Plate#	Tailing Factor
Levocetirizine Dihydrochloride	standard	5.158	2489093	2857	1.58
Levocetirizine Dihydrochloride	standard	5.152	2488474	2967	1.59
Levocetirizine Dihydrochloride	standard	5.149	2490182	2840	1.61
		5.153	2489250	2888	1.59
		0.081	0.035	2.391	1.098

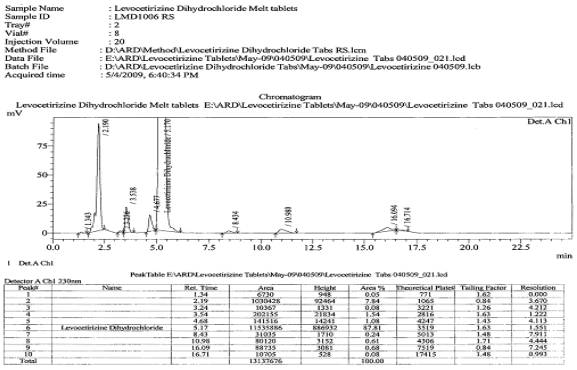
Figure 1(b)



<< Detector A >>
ID#1 Compound Name: Levocetirizine Dihydrochloride

Sample Name	Sample ID	Ret. Time	Area	Theoretical Plate#	Tailing Factor
Levocetirizine Dihydrochloride Melt tablets	LMD1006 Assay	5.150	2346109	3087	1.63
Levocetirizine Dihydrochloride Melt tablets	LMD1006 Assay	5.149	2343869	3149	1.64
		5.150	2344989	3118	1.64
		0.012	0.068	1.394	0.412

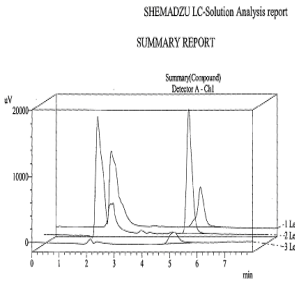
Figure 1(c)



Peak Table E:\ARD\Levocetirizine Tablets\May-09\040509\Levocetirizine Tabs 040509_021.lcd
Detector A Ch1 230nm

Peak#	Name	Ret. Time	Area	Height	Area %	Theoretical Plate#	Tailing Factor	Resolution
1		1.34	6730	948	0.05	771	1.62	0.000
2		2.19	1030428	92464	7.84	1068	0.84	3.670
3		3.24	10367	1231	0.08	3221	1.26	4.212
4		3.54	202155	21834	1.54	2816	1.63	1.222
5		4.68	141516	14241	1.08	4247	1.43	4.113
6	Levocetirizine Dihydrochloride	8.17	11535866	886932	87.81	5319	1.63	1.351
7		8.43	31035	1710	0.24	5013	1.48	7.911
8		10.98	80120	5152	0.61	4306	1.71	4.444
9		16.09	88735	3083	0.68	7519	0.84	7.245
10		16.71	10705	528	0.08	17415	1.48	0.993
Total			13137676		100.00			

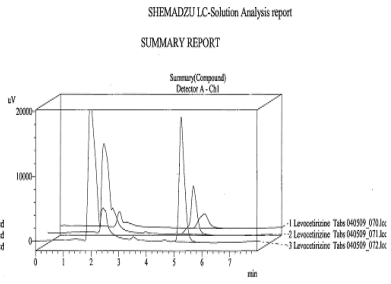
Figure 1(d)



<< Detector A >>
ID#1 Compound Name: Levocetirizine Dihydrochloride

Sample Name	Sample ID	Ret. Time	Area	Theoretical Plate#	Tailing Factor
Levocetirizine Dihydrochloride Melt tablets	LMD1006 Disso 10 min	5.253	102156	2685	0.97
Levocetirizine Dihydrochloride Melt tablets	LMD1006 Disso 10 min	5.246	255357	3273	1.48
Levocetirizine Dihydrochloride Melt tablets	LMD1006 Disso 10 min	5.165	41526	1167	1.39
		5.215	133013	2341	1.28
		0.851	82.853	45.861	21.331

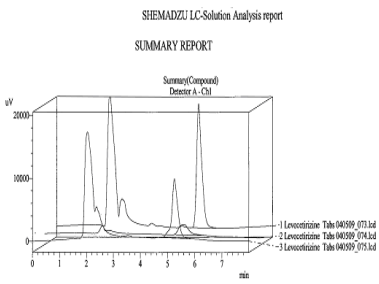
Figure 1(e)



<< Detector A >>
ID#1 Compound Name: Levocetirizine Dihydrochloride

Sample Name	Sample ID	Ret. Time	Area	Theoretical Plate#	Tailing Factor
Levocetirizine Dihydrochloride Melt tablets	LMD1006 Disso 20 min	5.199	52919	1167	1.11
Levocetirizine Dihydrochloride Melt tablets	LMD1006 Disso 20 min	5.246	134394	2933	0.95
Levocetirizine Dihydrochloride Melt tablets	LMD1006 Disso 20 min	5.247	251713	3559	1.52
		5.231	139675	2553	1.19
		0.532	72.869	48.576	24.398

Figure 1(f)



<< Detector A >>
ID#1 Compound Name: Levocetirizine Dihydrochloride

Sample Name	Sample ID	Ret. Time	Area	Theoretical Plate#	Tailing Factor
Levocetirizine Dihydrochloride Melt tablets	LMD1006 Disso 30 min	5.247	259402	3597	1.52
Levocetirizine Dihydrochloride Melt tablets	LMD1006 Disso 30 min	5.160	43154	1119	1.44
Levocetirizine Dihydrochloride Melt tablets	LMD1006 Disso 30 min	5.248	142337	3011	0.98
		5.218	147964	2576	1.31
		0.965	72.811	50.273	22.289

Figure 1(g)

Figure 1(a) HPLC chromatogram of levocetirizine dihydrochloride reference standard; 1(b) HPLC chromatogram of levocetirizine dihydrochloride sample; 1(c) of levocetirizine MIMTs (assay); 1(d) of levocetirizine MIMTs (related substance); and 1(e) of levocetirizine MIMTs tablet dissolution data at 10 minutes, 1(f) at 20 minutes, and 1(g) of at 30 minutes.

In-vitro *release kinetic studies, statistical evaluation and data fitting* [18-19]

A mean value of twelve determinations at each time point was used to assess the difference factor (f_1), the similarity factor (f_2), and the two indices of Rescigno (ξ_1 and ξ_2); while the mean value of six determinations was used to fit an *in-vitro* drug release profile of all formulation batches to different kinetic models so as to find their release exponents. Statistical analysis of per cent released data and other data were performed using one way ANOVA at significance level of 5%. Statistical evaluation, *in-vitro* release kinetic studies, non-linear least square curve fitting, data fitting, simulation, and plotting were performed with the Excel software (v 2007; Microsoft Software Inc, Redmond, USA) for getting parameters of each equation.

Accelerated stability studies

MIMTs in strip pack were stored at 30 ± 2°C/65 ± 5% RH and 40 ± 2°C/75 ± 5% RH in a stability analysis chamber and in a refrigerator (2-8°C) for a period of 12 week.[20] At 1 month, 2 months, and 3 months interval; MIMTs were withdrawn for analysis of appearance, hardness, moisture content, *in-vitro* dissolution test, content of active ingredient and related substances; and results were compared with respect to preliminary result (analysis result of samples prior to stability charging) and result of respective samples kept at 2-8°C.

RESULTS AND DISCUSSION

Used LH sample was white coloured crystalline powder with characteristic odour and highly bitter taste having specific rotation of $+10^o$ to $+14^o$, loss on drying value of 0.3%; and complies IP 2007 specification. LH possesses very poor flow properties and compressibility convincing for inclusion of granulation step in the formulation development process. Drug-excipient compatibility study reveals absence of interaction(s) between LH and proposed expcipients, as either any change in organoleptic properties with respect to control sample was not observed or statistically significant decrease in drug content and increase in related substance was not observed.

Wet granulation technique had eliminated tabletting problems, and improved flow property and compressibility to higher degree in comparison to the direct compression method. MIMTs prepared by wet granulation technique found to be superior to that prepared by direct compression technique, with respect to the pharmacopoeial product specifications. The values of evaluated pre-compression parameters were within prescribed limits and elicited free flowing property. A normal size distribution of granules was observed with the formulation batches prepared following wet granulation method while a skewed granule size distribution was observed with the formulation batch prepared following direct compression method. Uniformity of weight test was not performed as this test was not required for tablets that were subjected to uniformity of content test.[13]

Prepared MIMTs were white coloured smooth surfaced flat tablets without any pinholes or dimples. The data of post-compression parameters such as shape and size, hardness, friability, uniformity of content, uniformity of dispersion, wetting time, content of active ingredient, impurity profile, *in-vitro* disintegration time, *in-vitro* drug release kinetic data were presented with Table-3. Data of Table-3 reveals that tablets of all MIMTs formulation batches had comply almost all pharmacopoeial specifications.

Data of Table-3 reveals variation in thickness of tablets within the ± 5% of the average thickness value, while diameter of tablet reclines within the ± 1% of the average diameter value. The hardness values of all MIMTs formulation batches was found to be in the range of 41-49 Newton (Table-3). Excluding formulation batch F1 all formulation batches friability value lie below 1.0% w/w (Table-3) and complies the IP 2007 specifications, indicating robustness of the MIMTs having ability to withstand physical and mechanical stress during handling and transportation.

Study of *in-vitro* disintegration test result from Table-3 depicts that disintegration time values lies in the range of 15 to 118 s, for all formulation batches of MIMTs and were found to be within prescribed limit.[15] It was also observed that an increase in concentration of crosscarmelose sodium (Ac-di-sol) not only decreases disintegration time but also optimises the drug release profile. Ac-di-sol at a concentration of 30 mg per tablet acts as prospective disintigrant and results in disintegration of the tablet within three min fulfilling the criteria of MIMTs and has lowest value with respect to that prepared with 5, 10, and 20 mg. All MIMTs formulation batches had complied IP 2007 specifications for the uniformity of dispersion.

While the drug content of all MIMTs formulation batches was found to be between 90.9% and 99.1% of Levocetirizine Dihydrochloride (Table-3) indicating compliance of IP 2007 specification for the content of active ingredient value. It was also observed that all MIMTs formulation batches were complying IP 2007 specifications for uniformity of content.

Values of related substances from Table-3 reveals that all MIMTs formulation batches were complying IP 2007 specifications for related substances, as the individual impurity values were less than 1.0% and total impurities value was less than 2.0%.

Table 3: Values of evaluation parameters of all formulation batches and market sample (Lecociz MD).

Formulation code / Study parameter	F1	F2	F3	F4	F5	Market sample
Flow property of pre compression granules or powders	Fair	Good	Good	Excellent	Excellent	-----
Moisture content (%)*	3.14 ± 0.03	2.34 ± 0.04	2.69 ± 0.02	1.96 ± 0.05	1.34 ± 0.04	1.76 ± 0.01
Diameter (mm)*	6.02 ± 0.04	6.08 ± 0.07	6.11 ± 0.09	6.06 ± 0.05	6.01 ± 0.10	6.05 ± 0.06
Thickness (mm)*	4.6 ± 0.02	4.8 ± 0.04	4.15 ± 0.03	4.08 ± 0.01	4.11 ± 0.03	4.07 ± 0.02
Hardness (Newton)*	41 ± 3.1	49 ± 4.2	48 ± 3.8	43 ± 2.9	42 ± 3.2	44 ± 2.8
Friability (% w/w)	2.14	1.25	1.02	0.78	0.2872	0.68
Disintigration Time (s)	118	76	72	43	15	33
Uniformity of dispersion	Passes	Passes	Passes	Passes	Passes	Passes
Wetting Time (s)	180	158	112	56	22	46
Content of active ingredient (%)	90.9	91.1	94.3	99.6	99.1	99.1
Uniformity of content	Passes	Passes	Passes	Passes	Passes	Passes
Related substance						
Individual Impurity (per cent)	0.42	0.61	0.58	0.66	0.56	0.49
Total Impurities (per cent)	1.31	1.23	1.19	1.38	1.43	1.56
Zero-order kinetic constants						
Regression coefficient (r^2)	0.8213	0.7328	0.9892	0.9927	0.997	0.997
Proportionality constant (K_0)	2.0212	2.5939	3.7874	5.1065	4.0489	4.0489
First-order kinetic constants						
Regression coefficient (r^2)	0.6613	0.6324	0.635	0.6194	0.6167	0.6021
Release rate constant (K)	0.0238	0.2746	0.2757	0.2689	0.2678	0.2614
Higuchi model kinetic constants						
Regression coefficient (r^2)	0.9638	0.931	0.9371	0.9002	0.9464	0.9464
Higuchi constant (K_H)	11.867	15.846	16.771	16.619	17.522	17.522
Weibull model kinetic constants						
Scale parameter (α)	59.817	80.659	85.281	85.208	95.89	90.221
Shape parameter (β)	5.4453	10.456	9.3617	17.815	19.067	27.863
Location parameter (T_d)	2.1198	1.5218	1.6079	1.2834	1.2704	1.1754
Regression coefficient (r^2)	0.8585	0.9779	0.9619	0.9995	0.9573	0.1427

Note: * values with ± S.E.

Where K_0 was zero order proportionality constant, r^2 was the regression coefficient, K was the first order release rate constant, K_H was the Higuchi constant, a was the time scale of the process, β was the shape parameter, and T_d was the location parameter.

In-vitro dissolution and drug release profile data were studied with respect to the content of active ingredient value. All MIMTs formulation batches showed an average of 88 to 97% drug release at the end of 30 min with an individual values not less than 86.1% against IP 2007 limit of 75%, thus complies IP 2007 specifications for *in-vitro* dissolution.

Release exponent of model-independent and model-dependent approaches of MIMTs were listed in Table-3, which elucidates that the release mechanism of levocetirizine from MIMTs was statistically significant confined to zero-order kinetics, as plot of cumulative per cent levocetirizine release versus time were found to be linear and have highest regression coefficient (r^2) value (0.997) with respect to that of first-order and Weibull model; and was similar to that of market sample (Lecociz MD). Study of shape parameter values of Weibull model from Table-3 reveals that for all formulation batches the curve was sigmoid or S-shaped with upward curvature followed by a turning point (as β >1), while location parameter (T_d) values, characterises the time interval necessary to dissolve or release 63.2% of the drug present in the pharmaceutical dosage form, lies between 1.1754-2.1198 h.[18-19] Model-independent approach release exponents (f_1, f_2, ξ_1 and ξ_2) values of MIMTs of

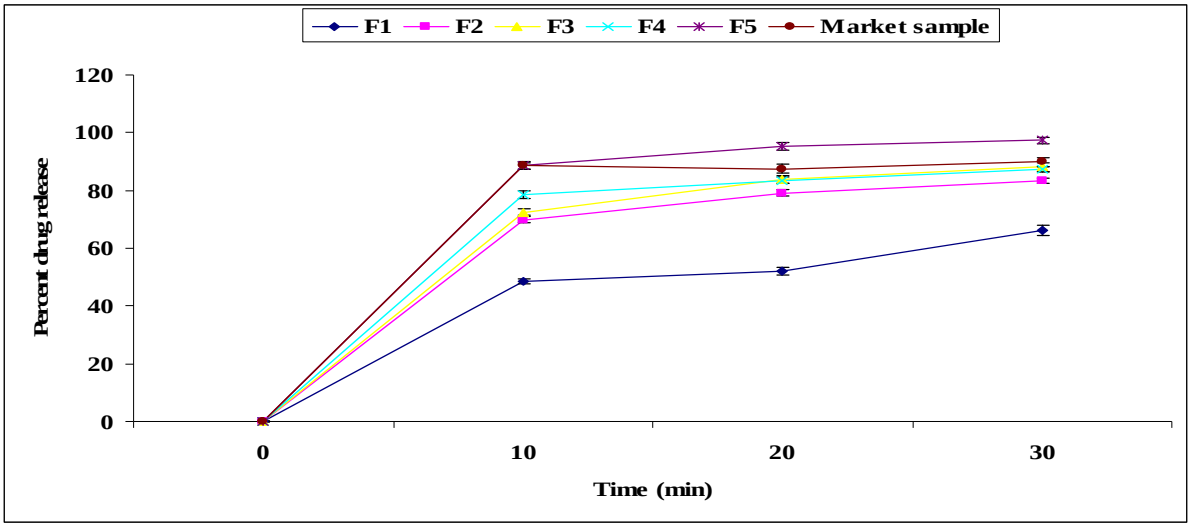
all formulation batches were listed in Table-4. Data of Table-4 depicts dissimilarity in *in-vitro* product performance of MIMTs for formulation batches F1 and F2 with respect to each other, other formulation batches and market sample.[18-19] While formulation F3, F4, and F5 had similar product performance with respect to each other and market sample, but formulation F5 was possessing highest degree of similarity with that of market sample.[18-19] It was also observed that formulation batch F5 requires shortest time to release 90% of total drug content whereas the other formulations requires more than 30 min to release 90% of total drug content.

Table-4: Mean value of model-independent approaches release exponents, i.e., dissimilarity factor (f_1), similarity factor (f_2) and two indices of rescigno (ξ_1 and ξ_2) of tablets. Data were presented as mean value, n=12.

Formulation pair	Model-independent release exponents			
	f_1	f_2	ξ_1	ξ_2
F1 versus F2	28	36	0.115	0.202
F1 versus F3	31.89	32.076	0.142	0.221
F1 versus F4	33.239	30.739	0.138	0.248
F1 versus F5	40.767	23.822	0.19	0.304
F1 versus MS	37.474	26.539	0.151	0.307
F2 versus F3	5	71	0.027	0.024
F2 versus F4	6.873	63.535	0.023	0.064
F2 versus F5	17.373	42.336	0.077	0.119
F2 versus MS	12.78	48.003	0.037	0.137
F3 versus F4	2.831	75.068	0.004	0.057
F3 versus F5	13.032	48.127	0.05	0.104
F3 versus MS	8.199	53.59	0.01	0.128
F4 versus F5	11.275	51.754	0.054	0.062
F4 versus MS	6.343	61.86	0.014	0.073
F5 versus MS	5	63	0.039	0.044

Where, MS stands for the market sample (Lecociz MD).

Figure 2: Comparative *in-vitro* dissolution profile (model dependent, Zero-order kinetic model) of all melt-in-mouth tablets formulation batches and market sample (Lecociz MD).



In-vitro release profile plot of cumulative per cent levocetirizine released versus time (Figure-2), of all formulation batches reveals that the rate of levocetirizine release from MIMTs depends on the variation in amount of Ac-di-sol.

MIMTs of formulation batch F5 exhibited product stability up to the investigational period of 3 month in strip packaging at stability conditions of 40°C ± 2°C/75% ± 5% RH, depicting adequate stability at room temperature and compatibility of levocetirizine and used excipients, as statistically significant diminished levocetirizine content and the variation of other parameters in tablets was not observed.

Experimental results evidenced that MIMTs of levocetirizine could be prepared successfully with reproducibility employing Doshion p-452 following complexation technique. To be specific, formulation batch F5 was found to be the most suitable formulation and was superior to other prototypes under development with regards to pharmacopoeial specifications and product performances, and having similar performance to that of market sample.

CONCLUSION

A stable crosslink polyacrilic resin complex system based levocetirizine MIMTs was successfully developed having *in-vitro* drug release characteristic that releases 90% of total drug content within 30 min. However, the developed product was less complex with regards to formulation components and processing aspects. These findings could be utilised for numerous drugs and might be considered resourceful in the applications.

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